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DEVELOPMENT OF VACCINE AGAINST CORONAVIRUS DISEASE 2019 (COVID-19) IN INDIA

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AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. Author RAR wrote the first draft of manuscript. Author TI framed and edited the manuscript. Author IR edited the manuscript. All the authors read and approved the final manuscript.

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Review Article

ABSTRACT

The pandemic declaration of Covid-19 infection by World Health Organization (WHO) and ensuing boundless morbidities and mortalities in practically all nations of the world prompted the innovative work to discover an immunization against SARS-CoV2 infection. Typically any new vaccine takes 10–15 y time. In pandemic circumstance, the whole cycle of vaccine development including clinical preliminaries gets shortened and optimized to 10–14 month time. i.e. the quest for vaccine against Covid-19 is going on at a high speed coming with the good news of two vaccines Covishield and Covaxin. This review aims at highlighting the present stages of development of vaccinesin Indian scenario.

Keywords: Coronavirus; covaxin; covishield; clinical; vaccines.

ABBREVIATIONS

ACE2 :*Angiotensin I-converting enzyme 2;*
CoV :*Coronavirus;*
CT :*Computed tomography;*
DPP4 :*Dipeptidyl peptidase 4;*
MERS-CoV :*Middle East respiratory syndrome coronavirus;*
N/A :*Not applicable;*
SARS-CoV :*Severe acute respiratory syndrome coronavirus;*
SARS-CoV-2 :*Severe acute respiratory syndrome coronavirus-2. https://doi.org/10.1371/journal.ppat.1008536.t001*.

1. INTRODUCTION

On 30th January, 2020 World Health Organization (WHO) declared a severe respiratory disorder syndrome which originated in Wuhan city as a global public health emergency and on 11th February named the disease as Covid-19. The pandemic declaration by WHO was made on 11th March 2020. Since the declaration of out-break of Covid-19, there is a race for development of a safe

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and effective vaccine against SARS-CoV2. Humans have suffered from lethal infectious diseases, including viral outbreaks, for a long time. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a newly identified virus that differs from severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) but can cause similar symptoms associated with pneumonia (Table 1) [1, 2]. The disease primarily affects the respiratory tract and disease severity can range from very mild rhinorrhoea to severe acute respiratory distress syndrome and death [3,4,5,6,7,8]. A substantial minority of infections are asymptomatic.

The main transmission route of SARS-CoV-2 from person to person is respiratory droplets or contact. Other possible routes include aerosol or oral-fecal transmission [9, 10]. An important epidemiological risk includes a history of travel or close contact with a patient with COVID-19 in the 14 days before symptom onset. Certain groups of the population, especially elderly men and those with underlying diseases, are more susceptible to SARS-CoV-2 infection [11,12,13,14]. Children, infants, and pregnant women are also reported to have SARS-CoV-2 infection [15,16,5,6,7]. Based on the first 425 confirmed cases, the mean incubation period of the virus is 5.2 days, with a 95th percentile distribution of 12.5 days, and its basic reproductive number is 2.2, which is lower than the 3.0 for SARS-CoV [3,4]. More recently, 2 studies showed that the mean incubation period of the virus is 3 days (range, 0–24 days) or 4.75 days (range, 3–7.2 days), respectively [12,3,4].

2. VACCINATION IMMUNOLOGY

To gain a better understanding of the clinical data, it is important to understand concepts in vaccine immunology. There is no “one size fits all” protective antiviral immune response. Every virus is different with different routes of infection, different range of infectable cell types, and different associated pathology. Accordingly, the immune response best suited for protection against each virus will also be variable [17]. Other factors such as sex, age, pregnancy, and route of infection can also influence the immune response [17,18]. It is widely reported that some people become heavily infected with SARS-CoV-2, but remain asymptomatic, and that some become critically ill and succumb to the disease. This extreme variability in response to infection underscores the variability of individual immune responses to this virus, suggesting that there may not be a single perfect strategy that will achieve uniform long-lasting immunity in everyone. The specific immune responses that elicit the most rapid and dependable viral clearance need to be understood and replicated by the vaccines. Major unanswered questions are whether humoral and/or cellular cytotoxic responses are required, what types of helper T cells are most effective (e.g. Th1 vs Th2 vs Th17) as well as what isotype of antibody response (e.g. IgG vs IgA) most effectively protects against this virus [19,7,20]. 26−28 Most of these questions are being answered through laboratory studies as well as through analysis of serum and circulating cells from recovered patients.

3. VACCINATION STRATEGIES

Many efforts have been directed towards the development of the vaccines against COVID-19, to avert the pandemic and most of the developing vaccine candidates have been using the S-protein of SARSCoV-2 [21]. In 2020, the worldwide SARS-CoV-2 vaccine landscape includes 158 vaccine candidates, out of which 135 are in the preclinical or the exploratory stage of their development. However Covaxin (Indian Council of Medical Resaerch) and Covishield (AstraZeneca) have been approved for vaccination drive. The vaccines which are in the conduit are based upon inactivated or live attenuated viruses, protein sub-unit, virus-like particles (VLP), viral vector (replicating and non- replicating), DNA, RNA, nanoparticles, etc. with each exhibiting unique advantages and hindrances [22]. To enhance the immunogenicity, various adjuvant technologies like AS03 (GSK), MF-59 (Novartis), CpG 1018 (Dynavax), etc. are now accessible to the researchers for the vaccine development [23,24]. The immuno-informatics approach is also used for the epitope identification for the SARS-CoV-2 vaccine candidates. It can be used to identify the significant cytotoxic T cell and B-cell epitopes in the viral proteins [25,26].

4. IMMUNITY VERSUS CORONAVIRUS

Immunity possesses an enmity with Coronavirus. Anti-Oxidant / Therapeutic Anti-Oxidants include Balanced diet combined with health supplements, herbs, green vegetables and citrus food. The most important activity of antioxidants is to prevent the attack of coronavirus as well as spreading of the Infection by quenching free radical also known as free radical scavenger. Green Tea as well as Black Coffee within specified limits helps the Patient for quick recovery. Smoking damages the lungs through a coating of nicotine directly and the patient is rapidly near the death by Pneumonic attack followed by

Table 1. Main differences between COVID-19, MERS and SARS

Epidemiology	**COVID-19**	**MERS**	**SARS**
Time of origin	December 2019	June 2012	November 2002
Place of origin	Wuhan, China	Jeddah, Saudi Arabia	Fushan, China
Has travel history	Yes	Yes	Yes
Confirmed cases	**99,388,894** (global)*	2,494	8,096
Death cases	**2,131,740** (global)*	858 (34%)	744 (9.2%)
Spread	Animal to human, then human to human	Animal to human, then human to human	Animal to human, then human to human
Main transmission	Airborne, contact	Airborne, contact	Airborne, contact
Patient-to-healthcare-worker transmission	Yes	Yes	Yes
Months of epidemic period	N/A	>39	8
Infection control risk	High	High	High
Current status	Active	A few new cases	No new cases
Incubation period (d)	4–7	2–15	2–14
Infectivity, basic reproductive number	1.4–6.47	0.3–1.3	2.2–3.7
Virology	**COVID-19**	**MERS**	**SARS**
Natural host	Bat	Bat	Bat
Intermediate host	Pangolins	Camels	Civets
Human host	SARS-CoV-2	MERS-CoV	SARS-CoV
Lineage	Beta-CoV lineage B	Beta-CoV lineage C	Beta-CoV lineage B
Genome size	29.9 kb	30.1 kb	27.9 kb
Receptor	ACE2	DPP4	ACE2
Clinical features	**COVID-19**	**MERS**	**SARS**
Principal symptoms	Fever, cough, fatigue, and shortness of breath	Fever, cough, fatigue, shortness of breath, and acute renal failure	Fever, cough, fatigue, and shortness of breath
Lab tests	Abnormal blood counts, abnormal coagulation, organ dysfunction, cytokine storm	Abnormal blood counts, abnormal coagulation, organ dysfunction, cytokine storm	Abnormal blood counts, abnormal coagulation, organ dysfunction, cytokine storm
CT scans	Bilateral patchy shadows or ground glass opacity in the lungs	Bilateral patchy shadows or ground glass opacity in the lungs	Bilateral patchy shadows or ground glass opacity in the lungs

Epidemiology	**COVID-19**	**MERS**	**SARS**
Severe cases	Sepsis and septic shock	Sepsis and septic shock	Sepsis and septic shock
Clinical management	**COVID-19**	**MERS**	**SARS**
Principal approach	Early supportive therapy and monitoring	Early supportive therapy and monitoring	Early supportive therapy and monitoring
Specific treatment	No	No	No
Vaccine	No	No	No

**As on January, 24, 2021*

sepsis which causes death. The key point of wellness is to maintain a good mental health to relieve stress during prolonged Lockdown period / under Quarantine condition. Sound sleep is a good secret of wellness,minimize the recovery time during attack of Covid-19.

5. VACCINES DEVELOPED IN INDIA

Coronaviruses are enveloped, positive sense single-stranded RNA viruses with a glycoprotein spike on the surface, which mediates receptor binding and cell entry during infection (Pang 2020). The roles of the spike protein in receptor binding and membrane fusion make it an attractive vaccine antigen. Almost all manufacturers are targeting spike protein as antigen apart from whole virion inactivated vaccine. There are multiple methods and platforms being tried for the development of this vaccine. Traditionally, vaccines are manufactured either as inactivated, live attenuated or subunit, but various institutions and manufacturers are trying next generation techniques. There are two different locally developed vaccines in India are approved for commercial use – COVAXIN (Bharat Biotech- ICMR), CoviShield (Serum Institute- ICMR) where as ZyCov-D (Zydus Cadilla [27] is under clinical trial. Therefore, it is imperative that the Indian government and companies strike licensing partnerships with such firms to manufacture the vaccine for use in India. India currently produces nearly 120 million doses of vaccines per month [28]. This capacity is being used for manufacturing a variety of vaccines targeting different diseases for domestic use as well global supply. This capacity cannot be entirely converted to producing COVID-19 vaccines, as the drop in availability of other vaccines would eventually result in increased burden of those diseases. A vaccine for COVID-19 cannot come at the expense of another disease outbreak in the future. Hence an increase in vaccine manufacturing capacity is imperative to meet the vaccine demand. Securing vaccine supply would include regulatory approval of vaccines for use in India, tying up with vaccine research institutions and increasing manufacturing capacities to align with demand requirements.

6. STAGES OF VACCINE DEVELOPMENT

There has never been a more rapid pace to vaccine development. The pandemic situation has been a challenge and a trigger to reconsidering the usual approaches to regulatory assessment and licensing processes. Vaccine companies are showing willingness to commit to scaled-up production prior to definitive phase 3 trial results [29].

Henceforth, Vaccine development consists of following steps: exploratory, preclinical and clinical stages. Exploratory stage deals with basic research in the laboratory regarding the conceptual idea and development of an antigen against the disease against which vaccine needs to be produced. It usually takes 2–4 y time.

Preclinical stage: This stage of development uses a platform of tissue culture or cell culture systems and animal testing to assess the safety of the candidate vaccine and its immunogenicity. Animal studies using mice, rabbits, guinea pigs, monkeys etc. according to the antigens, are used to find out the immune response and also side effects related to the candidate vaccine. These studies provide researchers an idea of the cellular responses they might expect in humans. They may also suggest the safest starting dose for the next phase of research as well as the safest method of administering the vaccine. Many researchers in this stage try challenging the animals with the offending organisms to find out the efficacy in preventing the infection or severity of the disease. This stage usually takes 1–2 y and out of 100 potential candidates, 6 usually pass through this stage. The regulatory authority is informed about the candidate vaccine with full data and the sponsor company for manufacturing and undertaking the next clinical stages are identified [30].

Clinical stages of development consist of at least 3 stages and the 4th post-marketing safety assessment is also mandatory.

Clinical trial phase I: In Phase I, a small number of healthy adult volunteers usually between 20 and 80 subjects are ad- ministered the candidate vaccine. If the vaccine is intended for children, researchers will first test adults, and then gradually step down the age of the test subjects until they reach their target. Phase I trial is usually an open label trial where both researchers and subjects are aware of what vaccine has been given. The aim of phase I trial is to assess the safety as well the type of immune response the candidate vaccine may produce. In some of the instances, in this stage, the participants are challenged with the pathogens under carefully monitored and controlled environment to find the real effect of the vaccine. The data is analyzed and if it shows promising result, the trial progresses to the next phase.

Clinical trial phase II: In Phase II vaccine trial, a larger group of several hundred individuals participate in testing. Some of the individuals may belong to the groups at risk of acquiring the disease. These trials are randomized and well controlled, and include a placebo group.

The goals of Phase II testing are to study the candidate vaccine's safety, immunogenicity, proposed doses, schedule of immunization, and route of administration.

Clinical trial phase III: In Phase III of the trial, vaccine safety in a large group of people is tested. If the chance of side-effects is 1:1000, then a sample size of approximately 60,000 subjects is to be included in the trial. In this stage the immunogenicity of the trial vac- cine is tested, e.g. production of critical level of antibodies/ cell-mediated immunity and also whether it prevents infection by the infecting agent as well as protects from the disease.

After a successful Phase III trial, the vaccine manufacturer shall submit application for biological license of the product to the licensing authority (in India, it is Drug Controller General of India). The licensing authority then physically verifies the vaccine and if satisfied, gives permission.

The licensing authority constantly monitors the adverse reactions following vaccination as a post-licensure process. Many manufacturing companies undertake a Phase IV trial for safety, efficacy and other potential uses which are optional studies after a vaccine is released.

In normal circumstances, the entire process of development of a new vaccine takes approximately 10–15 y time. However in pandemic situation, taking into consideration the urgency, there is overlapping of clinical trial phases and the entire process can be advanced to 12 mo–18 mo time [23].

7. CHALLENGES IN VACCINE DEVELOPMENT

There are several challenges in the development of any new vaccine including SARS-CoV2 vaccine. The novel SARS- CoV2 virus is fast undergoing drift and several genomic changes have been identified. The most effective way of confirming the efficacy of a vaccine is to challenge the subjects with the offending organism and observe the occurrence of the disease in vaccine recipients in comparison to control population. However, in Covid-19, this experiment shall be unethical since the disease is still evolving and there is no effective treatment for the disease. It is difficult to state at this time the safety and efficacy of the vaccines in development until Phase 3 clinical trial data are examined properly. It is still debatable whether neutralizing antibody is sufficient and what is the critical level of antibodies that are protective?. The T cell response and cell-mediated immunity of the vaccine may be required for efficacy of the vaccine which also needs to be answered in clinical trials. The amount of antigen dose, the number of doses, duration of immunity and need for booster needs to be answered. Presently all the trials are done on healthy individuals and would require proving in individuals who are at high risk including children, immunocompromised, senior citizens, diabetes, heart disease etc. The safety of the vaccine can only be judged when a large number of subjects are studied in different ethnic and geographical locations. Considering that a safe and effective vaccine will be available, equitable distribution for the most vulnerable shall be a major challenge. The logistics of procurement, supply, storage, cold chain and administration at community level shall be a gigantic task to fulfill. By the time a safe and effective vaccine against Covid-19 disease becomes available and logistics are sorted out, it may happen that the pandemic is already declining and may be over.

8. COVISHIELD VERSUS COVAXIN

India has approved two vaccines: Covishield and Covaxin, for emergency use to fight Covid-19 pandemic in the country. The mass vaccination drive has already begun in the country. Covishield is the same vaccine that is being used in other countries including the UK. India's approval for Covaxin is conditional as it is still "in the clinical trial mode". Here is a comparison between the two Covid-19 vaccines approved in India:

Covishield has been developed by the University of Oxford and British-Swedish pharmaceutical company AstraZeneca and is reportedly 90 to 95 percent effective if the two shots are parted by around 2-3 months. Developed by Bharat Biotech and clinical research body Indian Council of Medical Research (ICMR), Covaxin is an inactivated vaccine. It means that an inactivated virus is injected into a body trying to trigger an immune response. It is one of the oldest methods of vaccination. Covishield has been developed by the Oxford University scientists in collaboration with the pharmaceutical company AstraZeneca. In India, its trial was undertaken by the Serum Institute of India (SII), which is also manufacturing the Covishield vaccine for the mass vaccination drive. Covaxin has been developed by the indigenous vaccine developer Bharat Biotech in collaboration with the Indian Council for Medical Research (ICMR). Covishield vaccine has been developed by using the virus adenovirus that causes common cold infections among chimpanzees. Its genetic material is same as that of the spike protein of SARS-CoV-2 coronavirus. Spike protein is the part of SARS-CoV-2 using which the virus enters a human body cell. Covishield vaccine has been developed by

using a weakened version of the adenovirus. Covaxin vaccine has been developed using dead coronavirus — called "inactivated" vaccine in medical language. Under inactivated state, the virus is not capable of infecting people or replicating on its own inside the body of a person after being injected. But a shot of the vaccine prepares the immunity system to recognise the actual virus and fight it if and when infection happens. While Covaxin is still in the final stage of clinical trial and no efficacy rate has been made public for this Covid-19 vaccine, the efficiency of Covishield has been pegged at over 70 per cent. This efficacy rate is far below than the vaccines developed by Pfizer-NBiotech and Moderna, but it is above the qualifying efficacy benchmark of 50 per cent set by several countries [31]. Both Covishield and Covaxin are two-dose Covid-19 vaccines. But in an interesting development that was considered as inadvertent error, the Covishield vaccine was found to show over 90 per cent efficacy if one and a half doses are given to the recipient. However, in India, the SII conducted trials using full two-shot doses during testing. The two shots of the Covishield vaccine need to be spaced by six weeks. In the case of Covaxin, the interval between the two shots has not been yet prescribed by the Drug Controller General of India (DCGI) but its developer Bharat Biotech had earlier said the second shot would be given after 14 days. Both Covishield and Covaxin vaccines are easy to store as they require to be kept at 2-8 degree Celsius. Most vaccines commonly used in India are kept at this temperature range. This makes transport and local storage of both Covid-19 vaccines safe and easy for all parts of the country.

Currently the government is controlling the vaccination drive against Covid-19, and it is free. Different reports have cited different prices for both the vaccines. The Covishield vaccine is reported to cost the government around Rs 400-450 or Rs 200-225 per dose.

The pricing of indigenously developed Covaxin is not clear yet. However, some reports say the Bharat Biotech has priced its Covid-19 vaccine at Rs 350.

8.1 The Vaccination Plan

The government aims to vaccinate 30 crore people by July defining them as "priority population". They include frontline health workers, essential duty personnel and vulnerable sections of population. The first batch of 3 crore people will be given the shots of Covid-19 vaccines by March. Vaccination will be done through registration on Co-WIN, the digital platform developed by the government agencies to facilitate and monitor the drive against Covid-19 pandemic.

9. CONCLUSIONS

Vaccination is quite possibly the most practical systems for avoidance of illnesses. A protected and compelling immunization against SARS-CoV2 infection may be accessible before the finish of 2020 or start of 2021. Regardless of whether a protected and powerful antibody is accessible, it may not be conceivable to get the necessary number of dosages, cold chain support, cost and other conditions of mass immunization particularly in developing nations like India. With the public area putting intensely in the advancement of these immunizations, there are developing calls for widespread antibody availability. However nationalistic, topographical, and business components could disrupt the general flow. The immunization may not be the solitary panacea for the anticipation and halting of the pandemic, on the off chance that it precedes. We may need to follow general sterile measures including, hand wash, wearing cover, and avoid social gathering for some time before the pandemic of Covid-19 gets over.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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